第29章
Antipsychotic agents and Lithium

§ THE CLASSIFICATION OF PSYCHOTROPIC DRUGS

- Psychotropics
  - 會影響心情 (mood) 及精神機能，而改變心神 (mind turning)
- 依臨床使用分類如下:
  - 1. Antipsychotics (neuroleptics)
  - 2. Lithium & Other mood-stabilizing drugs
  - 3. Antidepressant (Thymoleptics)
  - 4. Antianxiety (Anxiolytics)
  - 5. Psychotomimetics

General concepts

- 精神病依臨床診斷可分為：

1. Neurosis :

(1) Anxiety states.

(2) Phobic reaction.

(3) Obesessive-compulsive reaction.

2. Psychosis :

(1) Organic psychosis.

(2) Functional psychosis.

a. Affective psychosis :

I. Manic-depressive states

II. Depressive illiness.

(I). reactive depression

(II). endogenous depression

– **b. Schizophrenia**.

  I. Simple schizophrenia.

  II. Paranoid schizophrenia.

(3) Psychopathic personality.

(4) Autism.

(5) Behavioral disorder in children.

(6) Sexual deviation

Mental disorder

- 由於環境對個體的影響
  → 造成個體生理變化 → 行為變化
- 由於遺傳的影響
  → 行為變化
- 由於藥物的影響
  → 行為變化

精神病依 diagnostic criteria 分為

1. Neurosis 精神官能症:

一般性格與正常人相同，患者知道自己有病，唯自己無法糾正，如：

(1) Anxiety states：對於迫在眉睫所產生的反應，有apprehension (憂慮)、fear (恐懼)。

(2) Phobic reaction

(3) Obsessive-compulsive reaction (強迫行為反應) (bizarre behavior)

2. Psychosis 精神病:

病人不知道行為與正常人不同:

(1) Organic Psychosis 器官性精神病

由下列原因所造成:

Cerebral arteriosclerosis

Mercury poisoning.

(2) Functional Psychosis 功能性精神病

由neurotransmitters之變化所造成:

- **Affective Psychosis (情感性精神病)**

此類病人常引起情緒改變。

a. Manic-depressive states :

情緒搖擺不定，有時呈現得意，有時則頹喪。

b. Depressive illiness (憂鬱症) :

(a) Reactive depression (反應性憂鬱症)：由於家庭變故，受打擊而出現傷慟 (bereavement)，有自殺傾向。

(b) Endogenous depression (內因性憂鬱症)：無可見原因引起者。

■ Schizophrenia精神分裂症

與Affective Psychosis 不同，精神分裂是心智分裂 (split mind)，具有delusion，hallucination; thinking, emotion (心情)，will (意志)，body-movement等不正常。

a. Simple schizophrenia (單純性): 發生於青春期或早期成年人，心情淡薄，不愛講話，人格漸漸腐化，變成與社會孤立，有如遭社會遺棄。

b. Paranoid schizophrenia (類偏狂，幻想症): 30歲以後發生，有明顯幻覺，長期服用amphetamine會造成此病。

※2014/6 更名為：思覺失調症**Schizophrenia**

- **Psychopathic personality: 為abnormal aggressiveness, 有攻擊性，侵略性，不負責任行為，對社會法律不關心，易犯罪。**
- **Autism (自閉症): 有不理人現象，年齡:自小孩到成年都有。**

- **Behavioral disorder in children:行為不正常小孩，活動力強 (hyperactivity), 不安 (restlessness), 性情暴躁(aggressiveness), 愈壓抑愈嚴重，叫做 hyperkinetic child syndrome.**

  治療用:

  a. Neuroleptics (haloperidol)

  b. Methylphenidate.

- **Sexual deviation (性異常)**

  虐待狂

  可用 anti-androgen 治療，為block androgen receptor 阻斷 androgen 活性→ cyproterone.

§ Pathogenesis of Schizophrenia (精神分裂症之病原)

→至今仍不清楚。

→由精神藥物之發展，反推精神病之成因。

1. 分子遺傳學假說:

→對家族遺傳學的研究包括雙胞胎的研究、領養的研究，証實精神病有強裂之遺傳傾向，尤其是精神分裂症、躁鬱症等。

→帶有精神分裂症基因之人，可能發病，也可能不發病 (10%); 發病與否常取決於某些因素，如壓力或藥物濫用等。

2. Dopamine Hypothesis:

→由於 dopaminergic activity 不正常所引起。

→1960年，Carlsson & Lindquist 首先提出。

◆ 理由:

＜1＞大部份 antipsychotic drugs 均可明顯的阻斷中樞神經系統

(特別是 mesolimbic-frontal system 間邊緣區-額葉)之D_2 receptors。

＜2＞增加dopaminergic activity 之藥物，會使schizophrenia 惡化

ex: levodopa (DA precursor)

amphetamines (release of dopamine)

apomorphine (a direct dopamine receptor agonist)

＜3＞利用positron emission tomography (PET) 檢測發現 schizophrenia

患者其腦中dopamine receptors 之密度均較正常人為高。

◆ 理由:

＜4＞未經 antipsychotic drugs 治療之 schizophrenia 患者其腦中 (特別是左半球 mesolimbic-frontal system 間邊緣區-額葉) dopamine receptors 之密度有增加之情形。

＜5＞1993年，Seeman et al. 發現 Schizophrenia 患者其紋狀體之 D_4 受體比對照組增加大約6倍。

Clozapine (antipsychotic drug) 對 D_4受體具高親和力。

schizophrenia是否與D_4基因變異之相關性仍有待進一步之研究。

[NOTE]:

◆ **腦部造影術 (Brain Imaging Techniques)**

＜1＞電腦斷層掃描 (CT) 與核磁共振 (MRI; 三度空間)

→可顯示活體腦內部的結構

＜2＞Positron Emission Tomography (PET)

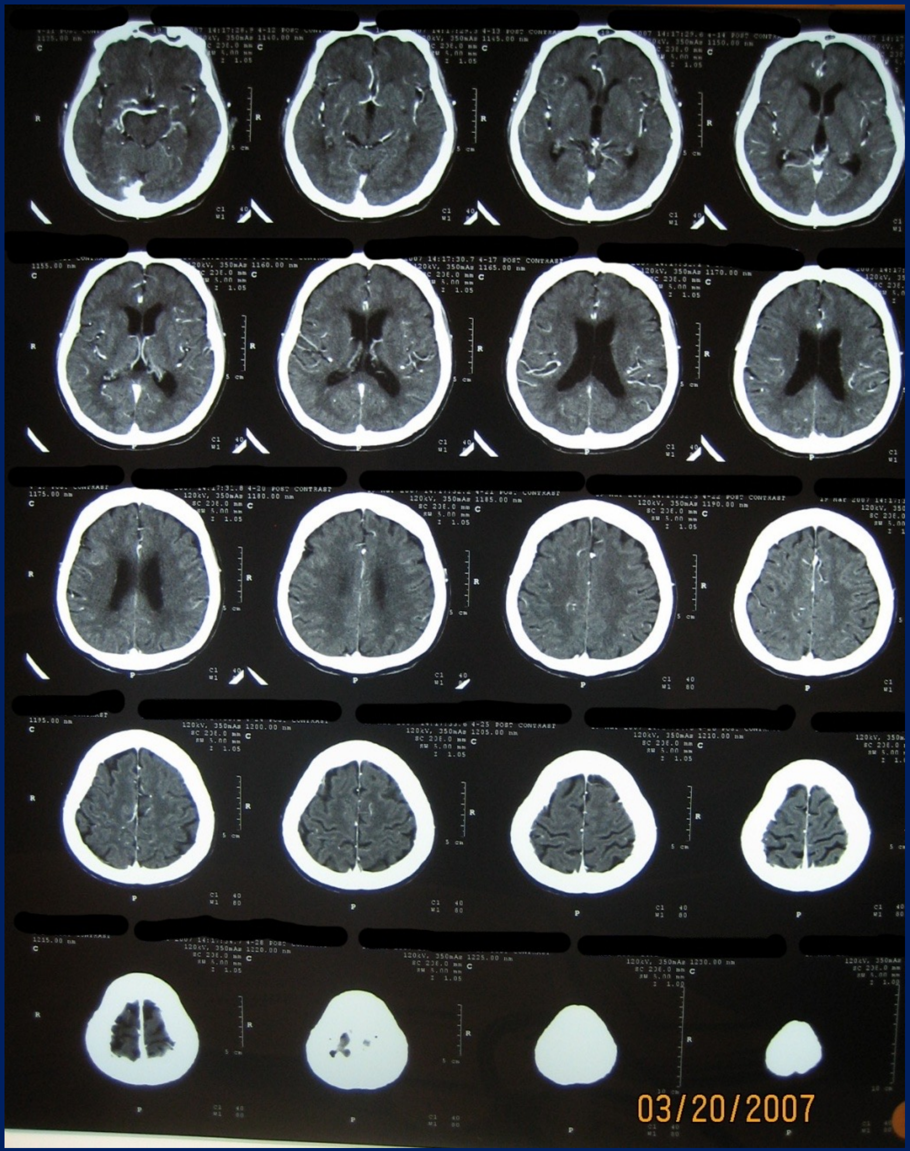
正電子發射斷層造影

→利用發射正電子的同位素作為標記物，將其引入腦內某一局部地區參與已知之生化過程，再利用現代斷層掃描技術將標記物所參與之特定代謝過程的代謝率以立體影像的形式表示出來。

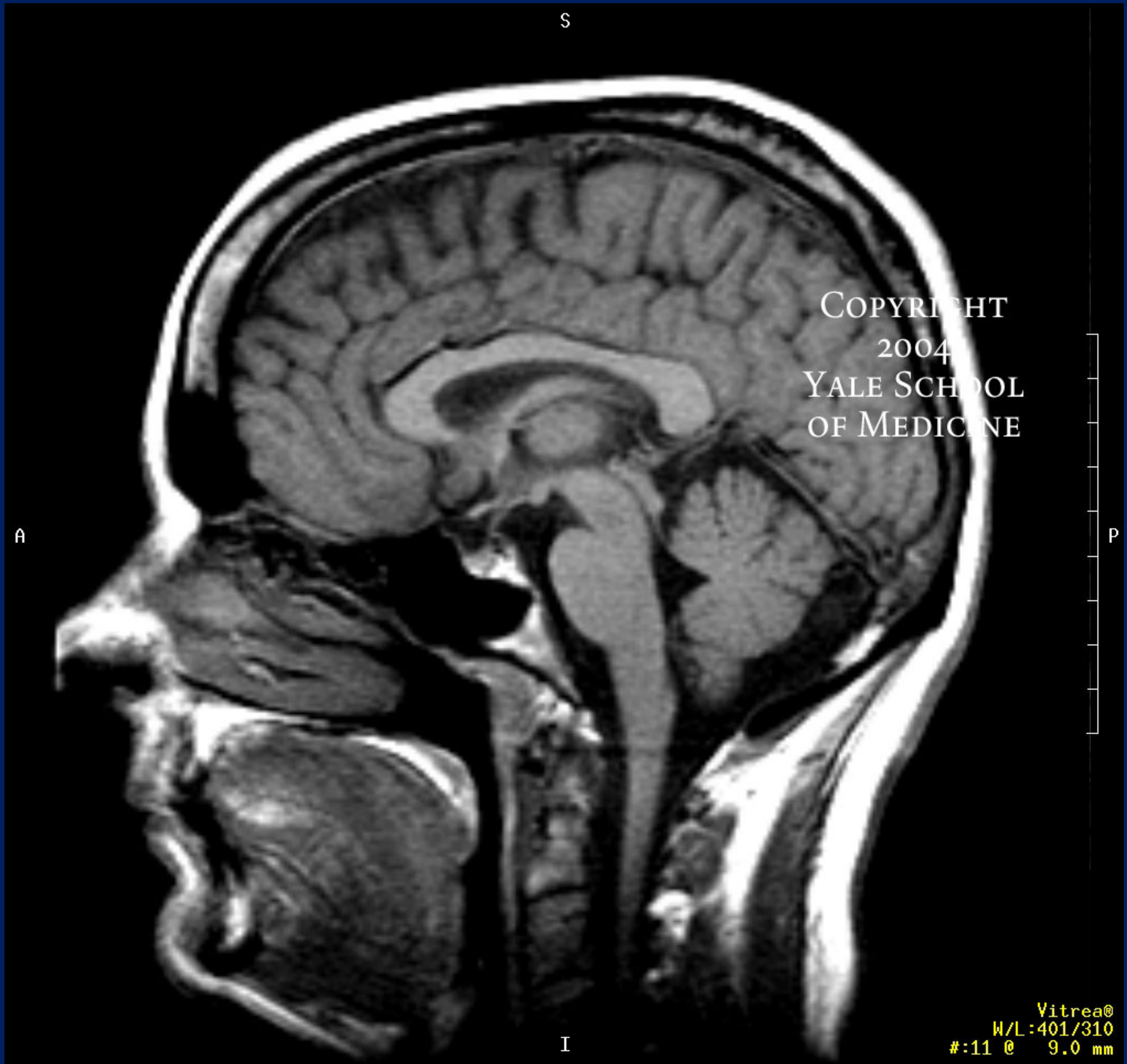
→主要是檢測腦內生化代謝與生理功能之變化

◆ **早期antipsychotic drugs對D_1, D_2, D_3 均具拮抗作用，專一性較低; 目前antipsychotic drugs 對D_2或D_4 receptors 之阻斷作用更強且更具選擇性。**

CT



MRI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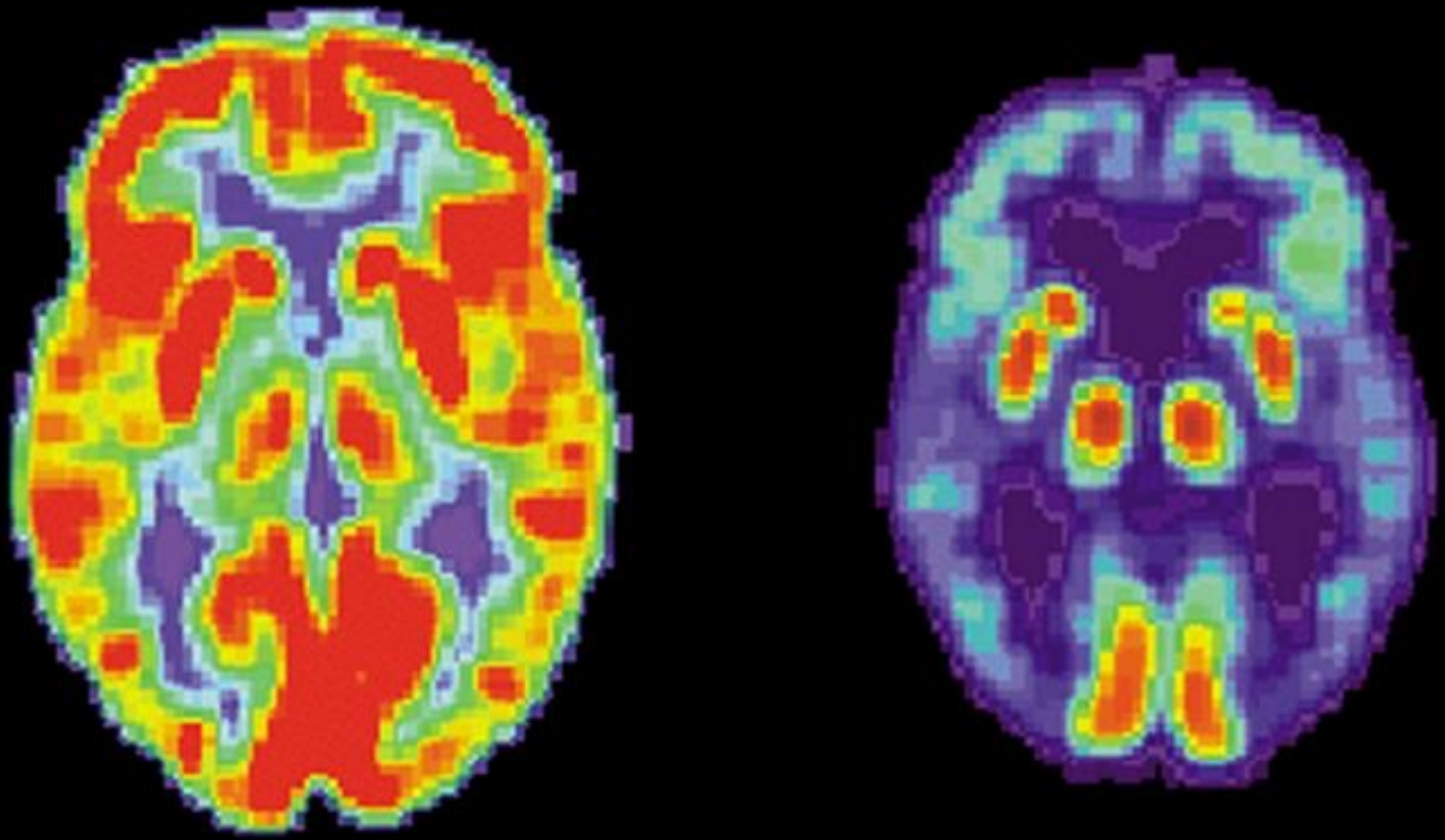
PET



3. Other Theories:

(1) 許多antipsychotic drugs除具 dopamine receptors 之阻斷作用外，

亦為5-HT_{2A} receptors antagonist (clozapine)

(2) 且 5-HT 對 dopamine pathway 具調節作用

⇒5-HT 可能與 schizophrenia 有關。

3. Other Theories:

(3) 許多抗精神藥除具 dopamine receptors 之阻斷作用外，亦是具有 $5\text{-}HT_{2A}$ receptors antagonist (clozapine)

(4) 又$5\text{-}HT_{2c}$ receptors 當 stimulation 時，可調節cortical 及 limbic dopaminergic activity。所以$5\text{-}HT_{2c}$ agonist 可開發新 antipsychotic agents.

(5) 又 glutamate 是興奮性腦內神經傳達物質，如 phencyclidine、ketamine 是NMDA (N-methyl-D-asparate) receptor之非競爭性抑制劑，會加強 schizophrenia病人之失智及psychosis。

因此LY2140023是 metabotropic 2/3 glutamate neceptor (mGLuR2/3) 之 agonist，可能對神精分裂症有效。

- 註：
  - 第一代 antipsychotics block D_2 receptor
  - 但第二代新抗精神病藥 clozapine
    對D_2 receptor low affinity,
    對 5-HT_{2A} high affinity

Treatment of Mental Disorder

1. Psychoanalysis (心理分析)

了解病因：如失意、家庭變故。

2. Insulin Shock：(造成30-60分之shock)

如病人有粗暴行為，使用insulin，使血糖↓→coma，腦部休息，恢復。
使用於schizophrenia, 但已不用，死亡率高。

3. ECT：

使用200-1500 mA之電流0.1-0.6秒，通過templs(額頭)，
→會產生幾秒之tonic convulsion
→再有30-60秒之clonic convulsion
→confusion, amnesia記憶喪失30-90分
→恢復(改善腦內的neurotransmitters，使之平衡)

Practice：在shock前
先使用light anesthesia (thiopentone)
及short acting muscle relaxant (suxamethonium)

4. Surgery：

針對腦部病變部位切除。

若切錯，無法挽回。

5. Pharmacotherapy：

對遺傳者效果差，須家人安慰。

臨床上，對於初使用antipsychotic，要考慮使用條件為副作用少者。

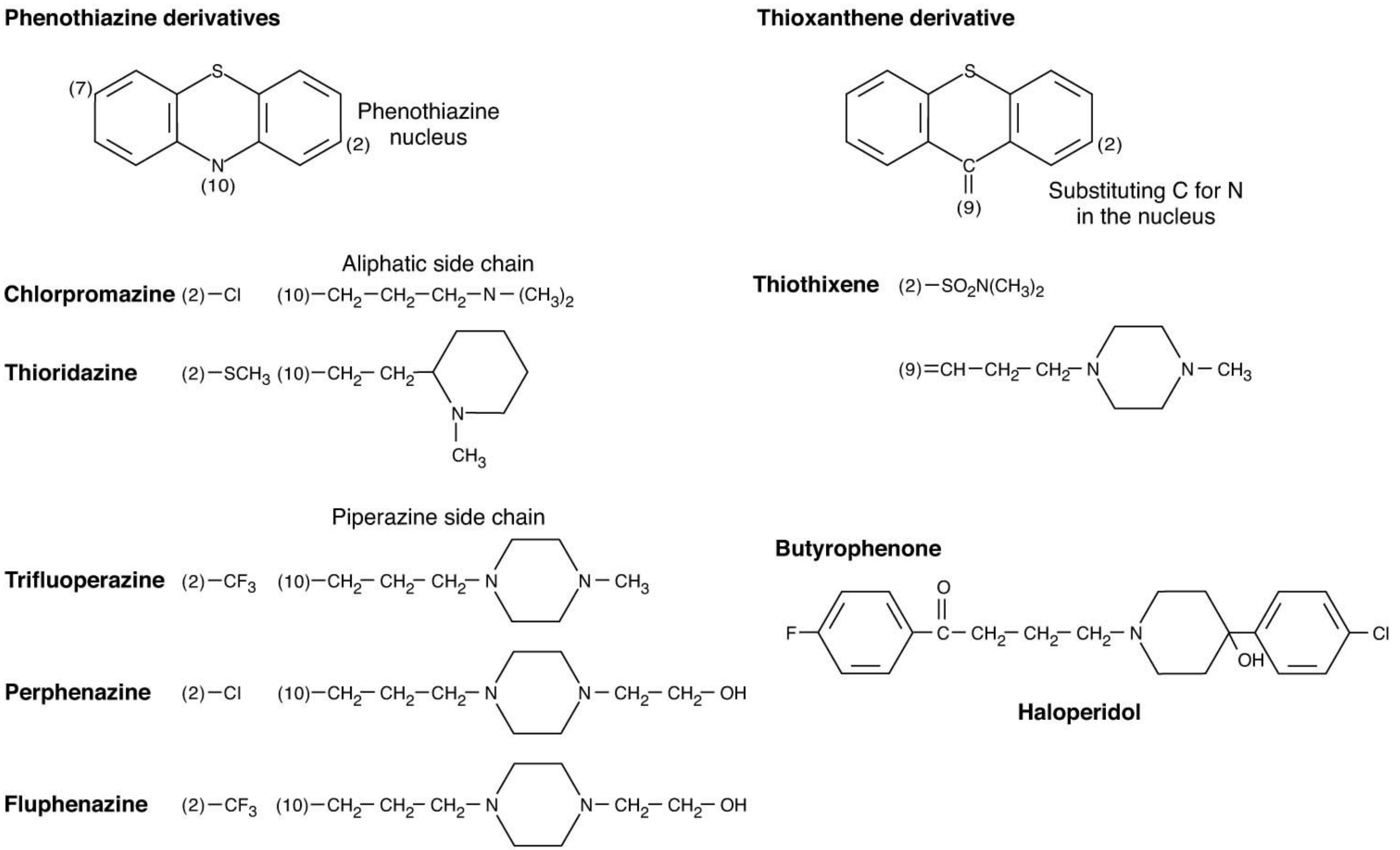
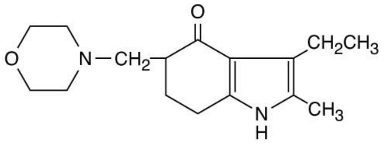
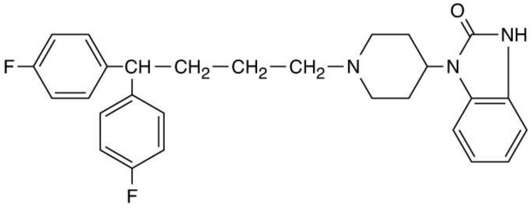


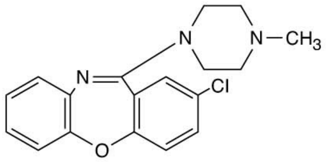
FIGURE 29–1 Structural formulas of some older antipsychotic drugs: phenothiazines, thioxanthenes, and butyrophenones. Only representative members of each type are shown.



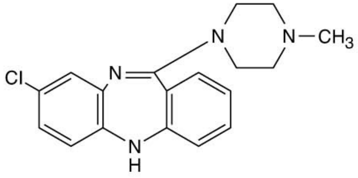
Molindone



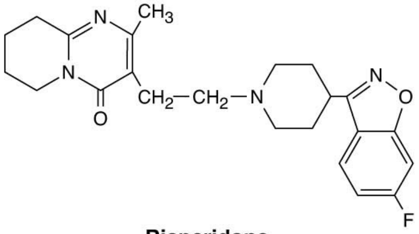
Pimozide



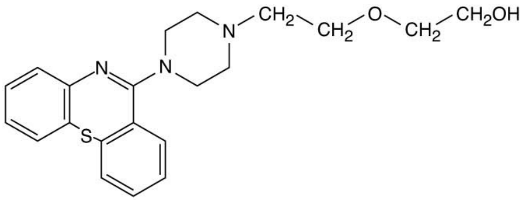
Loxapine



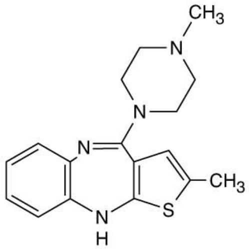
Clozapine



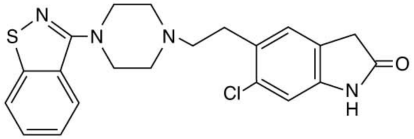
Risperidone



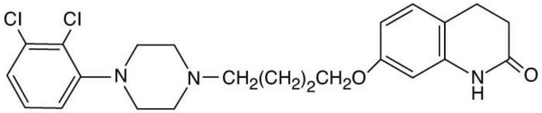
Quetiapine



Olanzapine



Ziprasidone



Aripiprazole

FIGURE 29–2 Structural formulas of some newer antipsychotic drugs.

TABLE 29–1 Antipsychotic drugs: Relation of chemical structure to potency and toxicities.

Chemical Class	Drug	$D_2/5\text{-}HT_{2A}$ Ratio[1]	Clinical Potency	Extrapyramidal Toxicity	Sedative Action	Hypotensive Actions
Phenothiazines						
Aliphatic	Chlorpromazine	High	Low	Medium	High	High
Piperazine	Fluphenazine	High	High	High	Low	Very low
Thioxanthene	Thiothixene	Very high	High	Medium	Medium	Medium
Butyrophenone	Haloperidol	Medium	High	Very high	Low	Very low
Dibenzodiazepine	Clozapine	Very low	Medium	Very low	Low	Medium
Benzisoxazole	Risperidone	Very low	High	Low[2]	Low	Low
Thienobenzodiazepine	Olanzapine	Low	High	Very low	Medium	Low
Dibenzothiazepine	Quetiapine	Low	Low	Very low	Medium	Low to medium
Dihydroindolone	Ziprasidone	Low	Medium	Very low	Low	Very low
Dihydrocarbostyril	Aripiprazole	Medium	High	Very low	Very low	Low

[1]Ratio of affinity for D_2 receptors to affinity for $5\text{-}HT_{2A}$ receptors.

[2]At dosages below 8 mg/d.

I. ANTIPSYCHOTICS(Neuroleptics)

- 主要用來治療精神分裂症，對某些精神病(Psychosis) 與精神過激狀態 (agitated states) 的治療亦有效。
  - 第一代抗精神病藥物:
    → Phenothiazine (Chlorpromazine) 及其衍生物 Thioxanthene。
  - 第二代抗精神病藥物:
    → Butyrophenone (Haloperidol) 1958年開始使用。
  - 第三代抗精神病藥物:
    → Benzamides (Remoxipride)
    - 對D_2 receptor 具選擇性 (blocker)。

※ Pharmacokinetics:

一、 **Absorption and Distribution**

→口服吸收通常不完全，肌內注射較佳。

·ex.chlorpromazine,thioridazine

oral dose → Systemie availability 25%-25%

·但 haloperidol

oral dose → Systemie availability 65%

※ Pharmacokinetics:

一、 Absorption and Distribution

→Half-life 長

·一般單劑量給予，一天一次。

·ex. Phenothiazines 之 piperazine 類

fluphenazine之酯化衍生物

(clinical potency 及Extrapyramidal toxicity皆強)

·但 Phenothiazines 之 aliphatic類

ex. chlorpromazine

→長期給予，最後一次給藥，數週後，尿中仍可檢出其代謝物。

二. Metabolism & Excretion

→在肝中代謝，由尿中排泄。

→有些藥物其代謝產物仍具活性:

ex. 1 7-hydroxychlorpromazine

ex. 2 reduced haloperidol

ex. 3 mesoridazine (metabolite of thioridazine)

作用較 thioridazine 強

※ Pharmacologic Effects

一、Mechanism of Action

A. Antipsychotic Drugs & Dopamine Receptors

1. dopamine receptor 可分為：

(1) D_1-like receptor group

→刺激 adenyl cyclase 產生 cAMP↑。

→D_1：存在 nucleus accumbens (積核)

→D_5：存在hippocampus, hypothalamus.

Pharmacologic Effects

一、Mechanism of Action

(2) D_2-like receptor group

→ 抑制 adenyl cyclase 產生 cAMP↓

block Ca^{++} channel;open k^{+}channel.

→ D_2：存在caudate, putamen (尾核、被殼)

D_3：存在frontal cortex, medulla,midbrain.

D_4：最新發現，在人體內具多型性 (polymorphism)

Pharmacologic Effects

一、 Mechanism of Action

2. D_2主要位於紋狀體，D_3、D_4位於limibic system
   此二區域在精神分裂症扮演重要之角色，因此大部分之
   antipsychotic drugs均為 D_2 、D_3 antagonist
3. antipsychotic drugs 之 therapeutic potency則與
   D_1 receptor 之親和力無關。

Table 30.1 Dopamine receptors

		D_1 type		D_2 type		
		D_1	D_5	D_2	D_3	D_4
Distribution	Functional role					
Cortex	Arousal,mood	++	-	++	-	-
Limbic system	Emotion,stereotypic behaviour	+++	-	+++	+	+
Basal ganglia	Motor control	++	+	+++	+	+
Hypothalamus	Autonomic and endocrine control	++	+	-	-	-
Pituitary gland	Endocrine control	-	-	+++	-	-
Agonists	Dopamine	+(low potency)		+(high potency)		
	Apomorphine	PA(low potency)		+(high potency)		
	Bromocriptine	PA(low potency)		+(high potency)		

PA=partial agonist

Table 30.1 Dopamine receptors

		D_1 type		D_2 type		
		D_1	D_5	D_2	D_3	D_4
Antagonists	Chlorpromazine	+	+	+++	+++	++
	Haloperidol	++	+	+++	+++	+++
	Spiperone	-	-	+++	+++	+++
	Sulpiride	-	-	+++	++	-
	Clozapine	+	+	+	+	++
Signal transduction		Increase cAMP		Decrease cAMP and /or increase IP_3		
Effect		Mainly postsynaptic inhibition		Pre-and postsynaptic inhibition Stimulation /inhibition of hormone release		
PA=partial agonist						

- Antipsychotic drugs之therapeutic potency:
  - 與D_1 receptor 之親和力無關 (不具線性關係)
  - 與D_2 receptor 之親和力有關 (具線性關係)

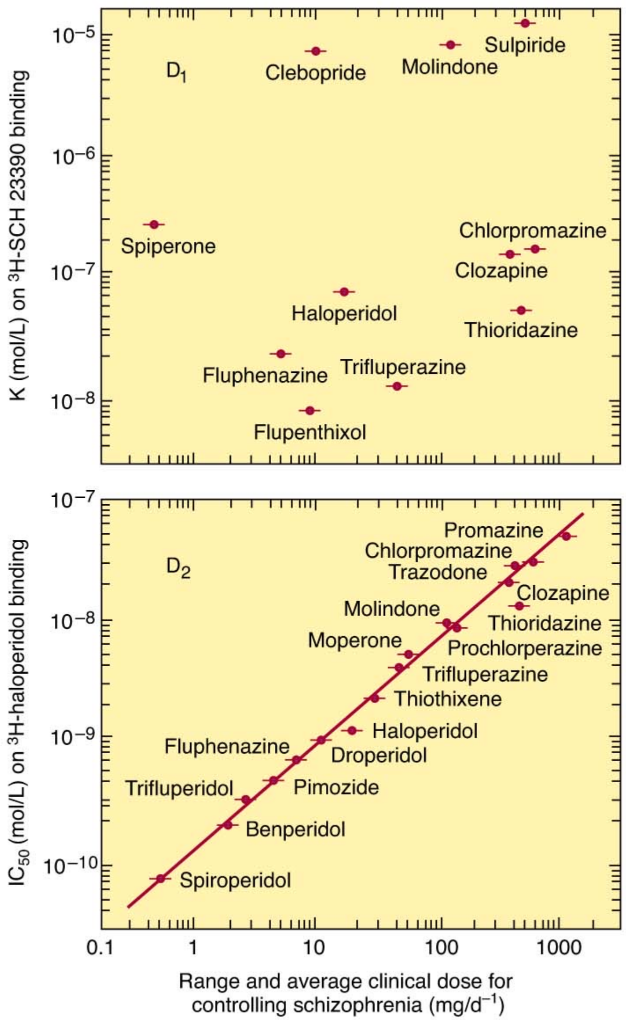


FIGURE 29–3 Correlations between the therapeutic potency of antipsychotic drugs and their affinity for binding to dopamine D_1 (*top*) or D_2 receptors (*bottom*). Potency is indicated on the horizontal axes; it decreases to the right. Binding affinity for D_1 receptors was measured by displacing the selective D_1 ligand SCH 23390; affinity for D_2 receptors was similarly measured by displacing the selective D_2 ligand haloperidol. Binding affinity decreases upward. (Modified and reproduced, with permission, from Seeman P: Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1987;1:133.)

§ Five Major Dopaminergic Pathway

(1) **Mesolimbic-mesocortical (皮質間質區) pathway**

→ cell bodies: substantia nigra.

→ project to: limibic system,neocortex.

→ function: 與行為有關

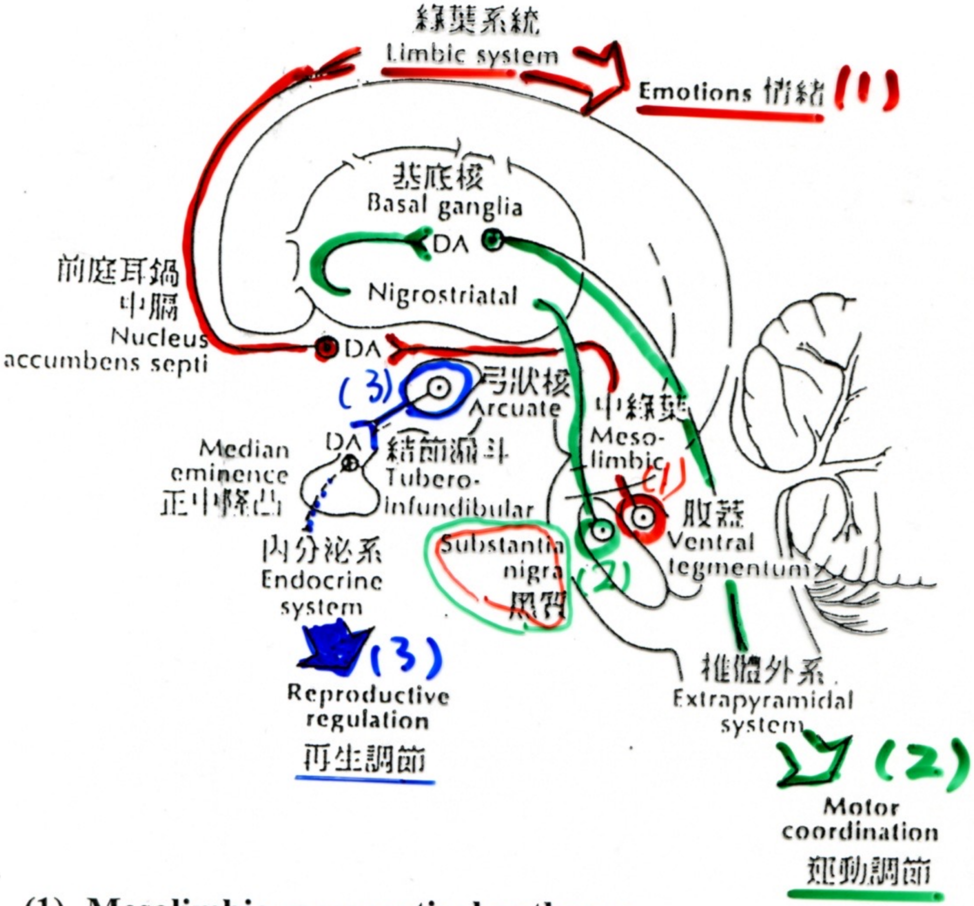
(2) **Nigrostriatal pathway**

→ cell bodies: substantia nigra.

→ project to: caudate putamen.

→ function: coordination of voluntary movement.

(自發運動之調和)



(1) Mesolimbic-mesocortical pathway

- substantia nigra → limibic system, neocortex.
- 與行為和情緒有關

(2) Nigrostriatal pathway

- substantia nigra → caudate putamen. (錐體外系)
- 與運動之調節有關

(3) Tubero-infundibular system

- arcuate nuclei → hypothalamus, posterior pituitary.

§ Five Major Dopaminergic Pathway

(3) **Tubero-infundibular system**

→cell bodies: arcuate nuclei,periventricular neurons.

→project to : hypothalamus,posterior pituitary.

→function: dopamine↑→inhibits prolactin secretion

(4) **Medullary-periventricular pathway**

→cell bodies:motor nucleus of the vagus.

→project to :未知?

→function : eating behavior

(5)Incertohypothalamic pathway

→cell bodies: hypothalamus.

→project to: lateral septal nuclei.

→function: 未知?

§與抗精神病藥物相關之Dopamine腦核與路徑

(1) Mesolimbic-mesocortical pathway

·substantia nigra → limibic system,neocortex.

·與行為和情緒有關

(2) Nigrostriatal pathway

·substantia nigra → caudate putamen (錐體外系)

·與運動之調節有關

(3) Tubero-infundibular system

·arcuate nuclei → hypothalamus,posterior pituitary.

·dopamine↑→ prolactin↓.

B. Block Limbic System DA Receptor:

(Limbic system是行為和情感中樞，包括舊皮質及新皮質)

※ 於1978年由Carllson 發表具有block DA receptor (Biol.Psychiatry)

※ 於1984年由Snyder 發表於 Science

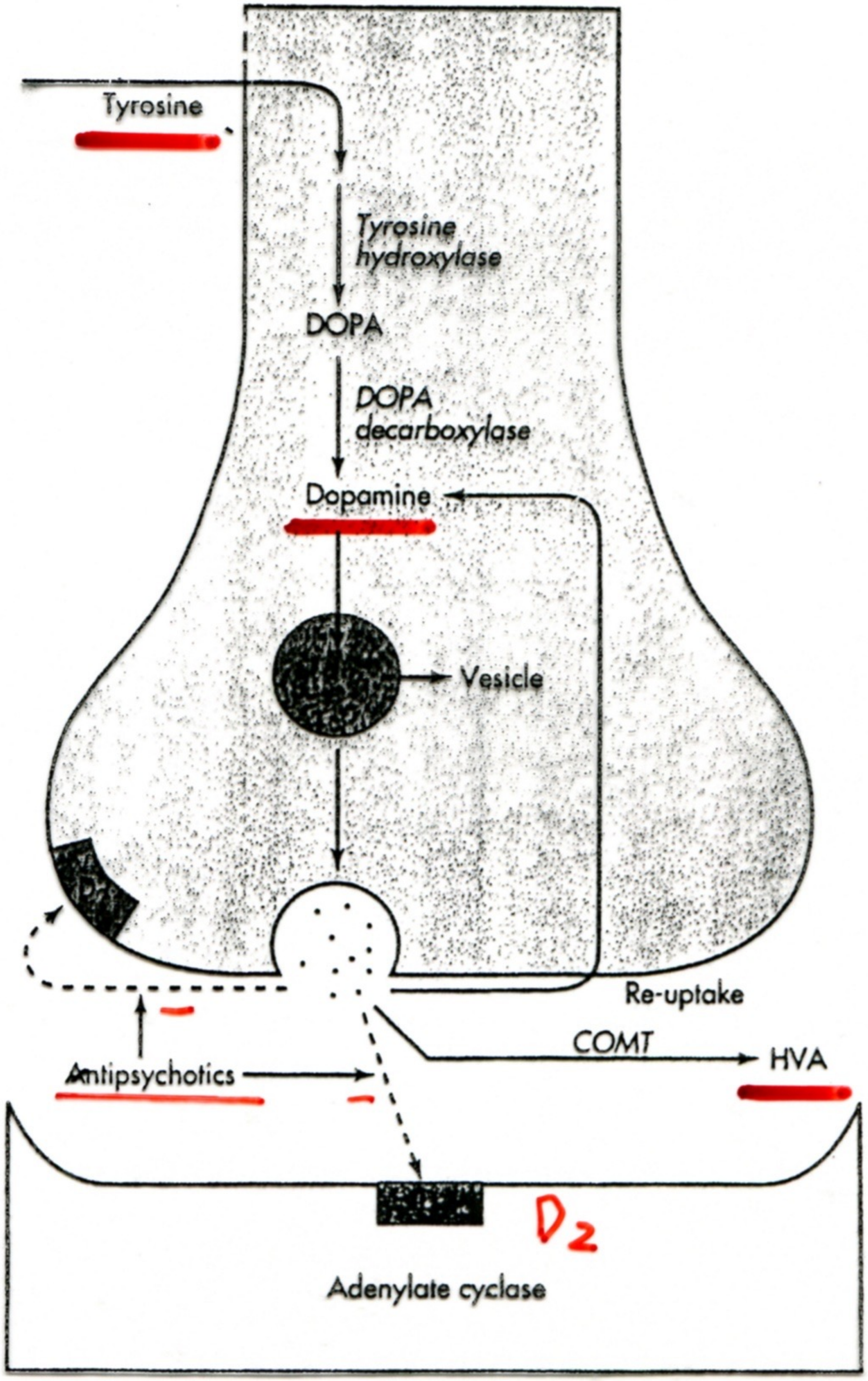
block D_2 receptor in mesolimbic & mesocortical pathway，即

striautm。亦即產生major motor side effect之理由。

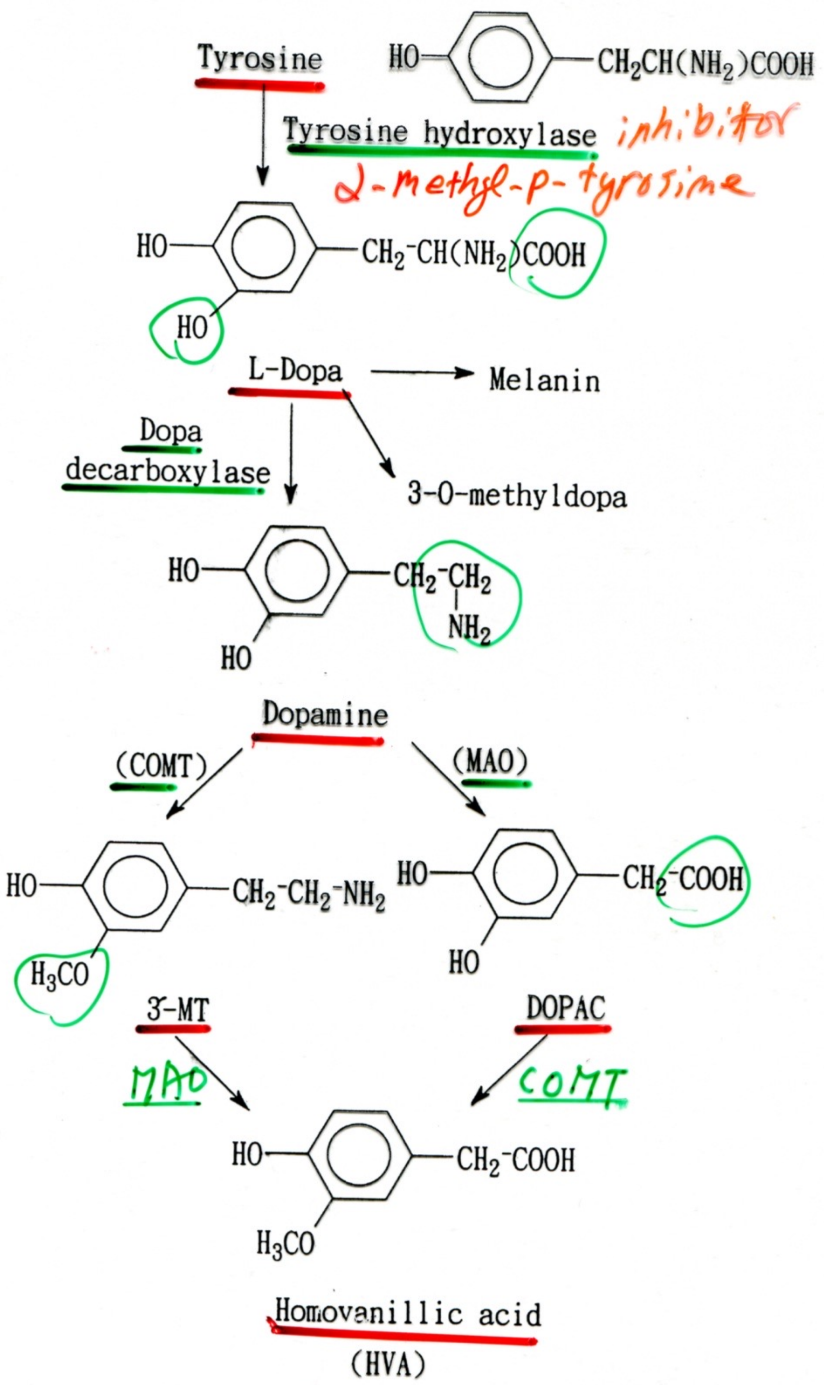
→因block receptor使pre-synaptic DA fiber 之 firing ↑

∴ 代謝率↑代謝物HVA↑

(feedback mechanism)



Tyrosine
Tyrosine hydroxylase
DOPA
DOPA decarboxylase
Dopamine
Vesicle
Re-uptake
COMT
HVA
Antipsychotics
D2
Adenylate cyclase


Tyrosine
HO-C6H4-CH2CH(NH2)COOH
Tyrosine hydroxylase
inhibitor
α-methyl-p-tyrosine
HO
CH2-CH(NH2)COOH
HO
L-Dopa
Melanin
Dopa
decarboxylase
3-O-methyldopa
HO
CH2-CH2
NH2
HO
Dopamine
(COMT)
(MAO)
HO
CH2-CH2-NH2
H3CO
HO
CH2-COOH
HO
3-MT
DOPAC
MAO
COMT
HO
CH2-COOH
H3CO
Homovanillic acid
(HVA)

B. Block Limbic System DA Receptor:

C. Activation of D_2 Receptor

→Ex. Amphetamines

levodopa

apomorphine

→motor activity↑, stereotyped behavior↑ (in rats)

→antipsychotic drugs screening test model.

→會加重 schizophrenia 症狀。

《Note》：

– Amphetamine 使DA release，因此能加重 schizophrenic symptoms.
– 若重覆使用，會引起
  paranoid schizophrenia (類偏狂)，
  但此效應可以被chlorpromazine所抵消。
– 巴金森氏症服用chlorpromazine後，會加重其病情

D. Differences Among Antipsychotic Drugs

※Receptor binding potencies (block)

Chlorpromazine:α_1=5-HT_{2A}>D_2>D_1

Haloperidol: D_2>α_1 > D_4 > 5-HT_{2A} >D_1 >H_1

Clozapine: D_4=α_1>5-HT_{2A}>D_2=D_1

Olanzapine: 5-HT_{2A}> H_1 > D_4 > D_2 >α_1> D_1

Aripiprazole: 5-HT_{2A} > D_2 = D_4 = α_1 = H_1

Quetiapine: 5HT_{2A}>H_1 > α_1 > $M_{1,3}$> D_2

Risperidone: 5HT_{2A}= D_2 > α_1 > $M_{1,3}$>H_1

Ziprasidone:5HT_{2A}= D_2 = α_1 >H_1

TABLE 29–2 Adverse pharmacologic effects of antipsychotic drugs.

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α-Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine-receptor blockade
	Tardive dyskinesia	Supersensitivity of dopamine receptors
	Toxic-confusional state	Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H_1 and 5-HT_2 blockade

二、 藥理作用

A. Psychologic effect (CNS):

→可以改善思想及行為之精神分裂。

→產生emotional quieting (情感平靜) 及psychomotor slowing 及affective indifference (情緒冷淡)。

→鎮靜作用。

B. Extrapyramidal effect:

→chlorpromazine如給予大劑量時，會引起錐體外作用，症狀有 tremor，rigidity (僵住)，akinesia (運動不能)，mask like face 及 hypersalivation。

→錐體外作用是由於DA receptor block，症狀如同parkinsonism ∴治療巴金森氏症藥，可以改善錐體外作用。

(1) benztropine,trihexyphenidyl (tremin) (Artane)
(為anticholinergic drugs).

(2) 1-dopa (DA precursor)

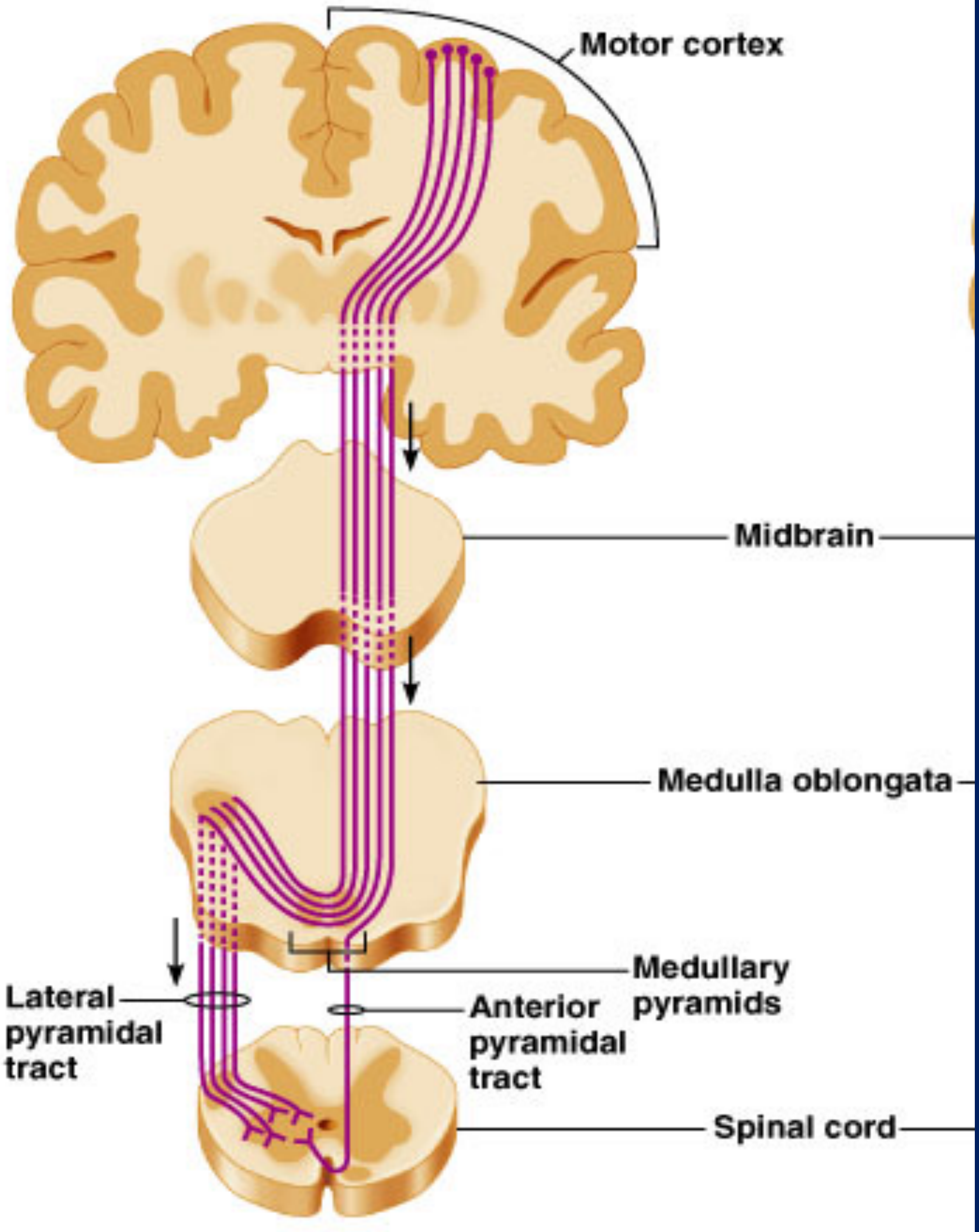
(3) bromocriptine: DA agonist(Receptor)

(4) Deprenyl: MAO-B inhibitor.DA $\xrightarrow{\text{MAO}}$ HVA
註： MAO-A inhibitor Moclobemide (antidepressant)

(5) Amantadine: 使DA從striatum釋放。

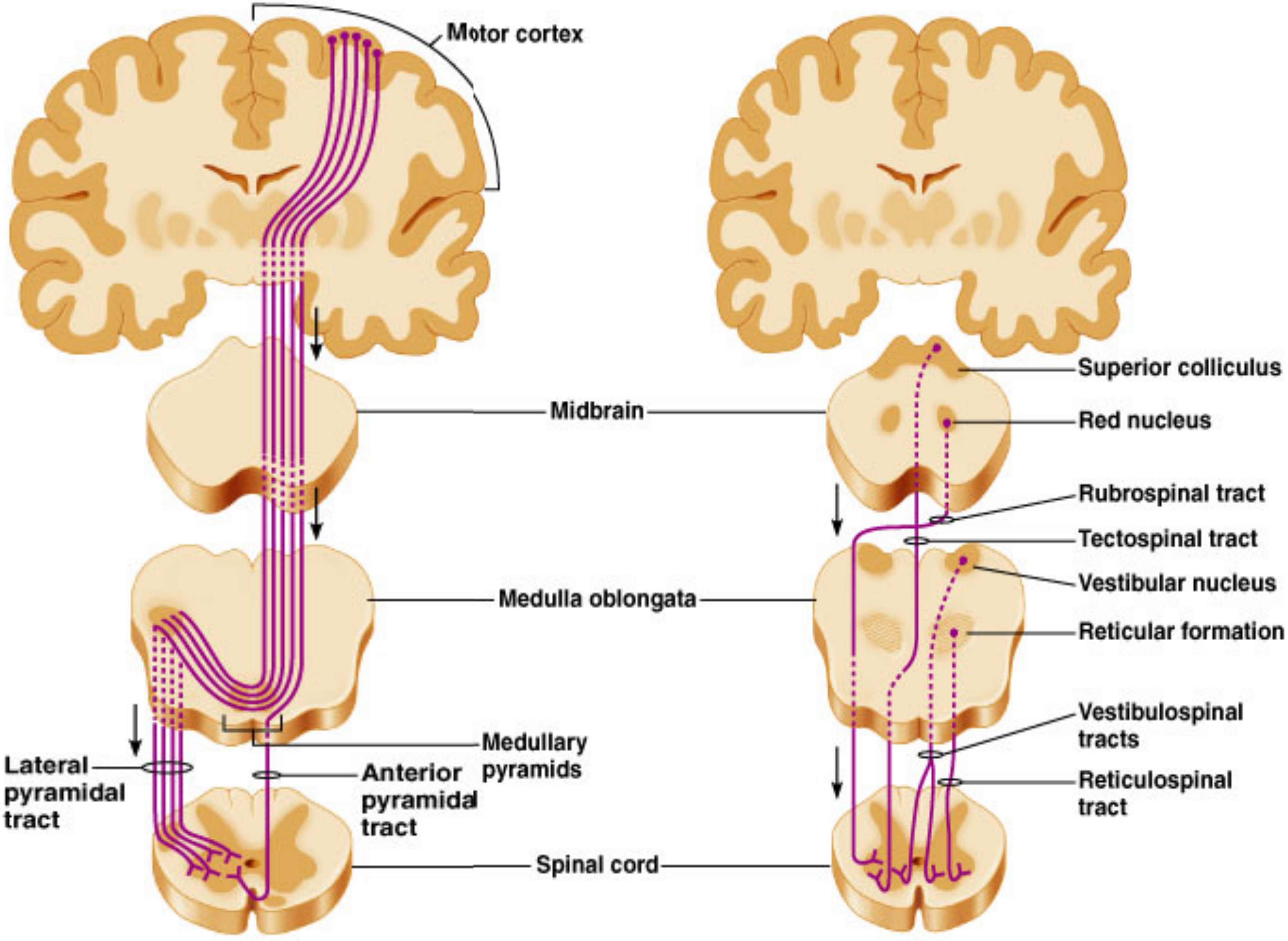
錐體外症候群

- **錐體**是從運動皮質區(motor cortex)到脊髓的通道。
  - 起源於大腦皮質區，經中腦(midbrain)、延腦(medulla oblongata)結束於脊髓(spinal cotd)。
  - 主要是控制細微的運作，特別是**前臂**、**手**、**手指**等。



(a) Pyramidal tracts

- **錐體外路徑**包括了所有錐體以外的運動控制路徑。
  - 主要作用在**軀幹**、**頸部**、以及**四肢**靠近軀幹的部分。
  - 控制了較大範圍的肌肉，讓他們一起收縮來保持身體的姿勢以及平衡。



(a) Pyramidal tracts

(b) Extrapyramidal tracts

錐體外症候群
(Extrapyramid syndrome EPS）

- 是指控制運動之系統受到影響所引起的症狀
  - 肢體發 抖，僵硬或不平衡感等。
  - 外錐體是協助錐體(pyramid system,運動系統）的副運動系統，當這個系統出了問題，吾人所做的動作就不會靈活。
  - 引起 EPS 的原因有藥物副作用 ，中風，腦瘤，退化，等等。

C. Anticholinergic & antiadrenergic effects (Autonomic nervous system):

→有弱抗膽鹼作用(atropine-like effect)
口乾，便秘，尿滯留，視力模糊，減少胃酸分泌，胃腸蠕動，減少出汗，散瞳 (mydriasis)

→有α-adrenoceptor block 作用 ，射精不能 (inhibition of ejaculation) B.P.↓ (姿態性低血壓)，反射性心跳↑

→DA blockade停經後乳漏，hyperprolactinemia、不育、性慾↓，將androgen轉變成estrogen。

註：

Phenothiazine (trifluoperazine)：是muscarinic及 α-adrenoceptor blockade

D. Cardiovascular effect

→ 姿態性低血壓(α-blockade)

→ 血管擴張⇒↑冠狀動脈血流量

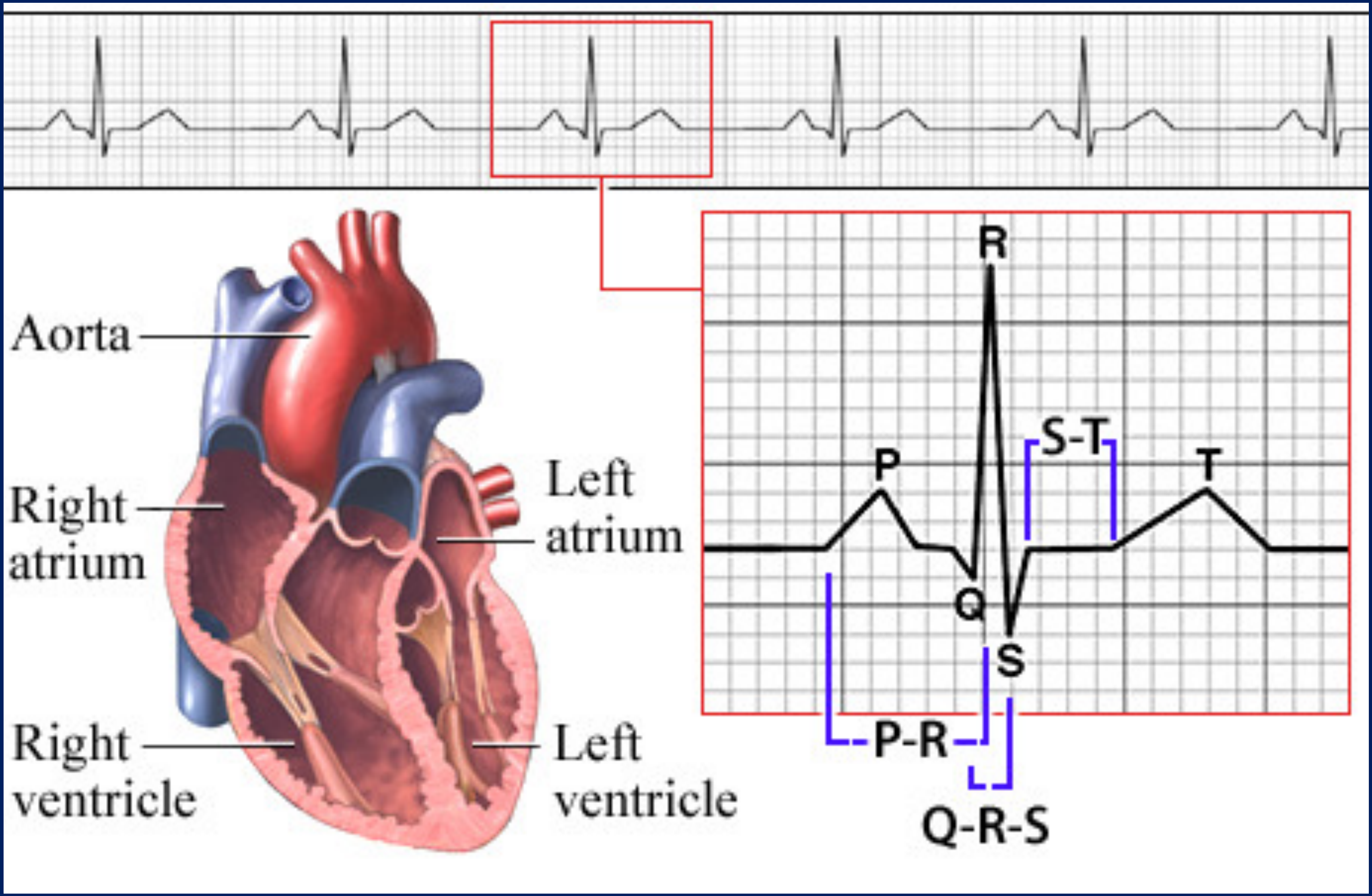
→ quinidine-like action (thioridazine).

⇒延長P-R, QRS, Q-T interval.

壓低S-T segment.

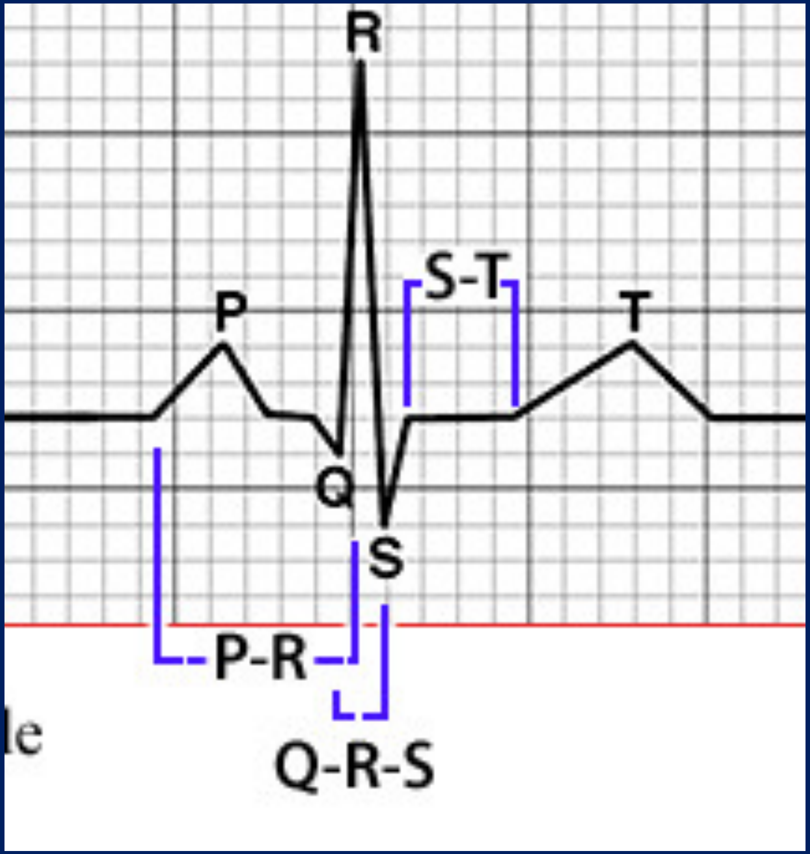
⇒心律不整

EKG


Aorta
Right atrium
Right ventricle
Left atrium
Left ventricle
R
P
Q
S
T
S-T
P-R
Q-R-S

EKG- Quinidine

正常



抗精神病藥

延長P-R, QRS, Q-T interval.

壓低S-T segment.

E. Temperature regulation:使體溫↓。

→抑制下視丘（體溫調節中樞）之DA receptors

→周邊血管擴張

F. Antiemetic effect:

→作用於 chemoreceptor trigger zone（CTZ），有抗吐作用，具有減緩動暈症(motion sickness)所引起的嘔吐作用。

→使用於尿毒、放射治療頭暈、孕婦嘔吐。(25 mg, tid)

Cardiovascular Effects of Antipsychotic Drugs

Phenothiazine:

- **Phenothiazines: high-dose (low potency), 高劑量 (低效價)**

  A. Orthostatic hypotension

  B. High resting pulse rate

  C. Mean arterial pressure & peripheral resistance↓

  D. Stroke volume ↓

  → due to autonomic actions

  (1) muscarinic cholinoceptor blockade

  (2) α receptor blockade

Cardiovascular Effects of Antipsychotic Drugs

E. Abnormal EKGs

Especially: thioridazine

(1) Prolongation of QT interval

→↑ risk of arrhythmias

EX 1: sertindole

EX 2: ziprasidone

(2) Abnormal configuration (形狀) of ST segment and T waves

→ reversed by withdraw

G. Endocrine effect:

→作用於 hypothalamus，

能 depress the release of the prolactin-release-inhibiting hormone↑

∴induce lactation↑

→又depress gonadotropin (性腺刺激素) output.

∴抑制排卵，月經閉止(amenorrhea)。

→corticotropin↓

∴adrenocorticosteroid↓

→又growth hormone↓

→又使食慾↑，體重↑。

H. 利尿作用:

→∵仰制 ADH，直接作用於腎小管，阻止水及電解質的再吸收。

I. Animal Screening Test:

→Inhibition of conditioned avoidance behavior

→Inhibition of amphetamine- or

apomorphine-induced stereotyped behavior

§ CLINICAL PHARMACOLOGY OF ANTIPSYCHOTIC AGENTS

- **Clinical Use:**

A. Psychiatric indications

1.Treatment of schizophrenia:

Antipsychotic drugs can reduce hyperactivity, bizarre ideation (怪異的想法), hallucinations (幻覺), and delusions (妄想).

§ *CLINICAL PHARMACOLOGY OF ANTIPSYCHOTIC AGENTS*

◆ **Clinical Use:**

A. Psychiatric indications

2. Antipsychotic drugs 亦可用來治療:

(1) Manic episode (偶發性狂燥)

(2) Psychotic symptoms of schizoaffective disorders

(3) Tourette syndrome

→Gilles de la Tourette's disease

(運動性共濟不能，伴有模仿言語及穢褻言語)

→可用Molindone 治療 (第三代抗精神藥)

§ *CLINICAL PHARMACOLOGY OF ANTIPSYCHOTIC AGENTS*

- **Clinical Use:**

A. Psychiatric indications

2. Antipsychotic drugs 亦可用來治療:

(4) Toxic Psychosis caused by overdosage of CNS stimulants.

(5) Phencyclidine intoxication

(6) Alzheimer type 的老年癡呆症所引起之行為紊亂

妥瑞氏症（Tourette's Syndrome)

- 是一種發病於兒童的慢性神經精神異常。
- 它與強迫症(憂鬱症)、焦慮症並存。
- 有易分心、過動等問題，常有突然短暫性動作、發出清喉嚨、吐口水、尖叫等雜音。

Drug Choice of Antipsychotic Drugs

- **Best guide for selecting a drug：patient's past responses to drugs**

- **Potency of drug**

  A. Low potency：Chlorpromazine、thioridazine

  B. High potency：thiothixene、haloperidol、fluphenazine

Drug Choice of Antipsychotic Drugs

- **Clozapine**

  ∵Side effects: agranulocytosis (粒性白血球缺乏症) &
  seizures threshold↓

  ∴僅用於下列病患

  A. failed to response to substantial dose (相當大的劑量) of conventional antipsychotic drugs

  B. have disabling tardive dyskinesia (遲發性異動症)

Drug Choice of Antipsychotic Drugs

- **Miscellaneous Derivatives (第三代)**

  Ex 1: Olanzapine　　　　Ex 2: Ziprasidone

  A. Provide the first line of treatment

  → superior side effect

  → low (absent) risk of tardive dyskinesia

  → olanzapine adverse effect：acute dystonic reaction (急性肌張力不足)、體重增加、seizure threshold↓

  → olanzapine可用於pregnant p't有bipolar disorder

  → ziprasidone：5-HT_{2A} (in brain partial agonist)不引起錐體外症候群，但會有QT prolongation。

B. Nonpsychiatric indications

1. Antiemetic effect:

→Antipsychotic drugs 除 thioridazine外均具止嘔作用。

ex. Prochlorperazine.

→作用機轉:

由於dopamine receptor blockade.

*CNS: inh. CTZ of medulla.

*Peripherally: inh. receptor in stomach.

2.Antipruritus (止癢):

→phenothiazine類藥物中side chain 較短者

→作用機轉 (chlorpromazine)

H_1receptor blocking action.

B. Nonpsychiatric indications

3. Preoperative sedatives(手術前鎮靜):

→ex. promethazine

4. Innovar:

Droperidol 與fentanyl配合使用，之商品名稱。

具有neuroleptic & antiemetic properties(Neuroleptanesthesia)

fentanyl 0.05 mg/ml

droperidol 2.5 mg/ml

in a 2 ml Amp.

TABLE 29–3 Some representative antipsychotic drugs.

Drug Class	Drug	Advantages	Disadvantages
Phenothiazines			
Aliphatic	Chlorpromazine[1]	Generic, inexpensive	Many adverse effects, especially autonomic
Piperidine	Thioridazine[2]	Slight extrapyramidal syndrome; generic	800 mg/d limit; no parenteral form; cardiotoxicity
Piperazine	Fluphenazine[3]	Depot form also available (enanthate, decanoate)	(?) Increased tardive dyskinesia
Thioxanthene	Thiothixene	Parenteral form also available; (?) decreased tardive dyskinesia	Uncertain
Butyrophenone	Haloperidol	Parenteral form also available; generic	Severe extrapyramidal syndrome
Dibenzoxazepine	Loxapine	(?) No weight gain	Uncertain
Dibenzodiazepine	Clozapine	May benefit treatment-resistant patients; little extrapyramidal toxicity	May cause agranulocytosis in up to 2% of patients; dose-related lowering of seizure threshold
Benzisoxazole	Risperidone	Broad efficacy; little or no extrapyramidal system dysfunction at low doses	Extrapyramidal system dysfunction and hypotension with higher doses
Thienobenzodiazepine	Olanzapine	Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction	Weight gain; dose-related lowering of seizure threshold
Dibenzothiazepine	Quetiapine	Similar to olanzapine; perhaps less weight gain	May require high doses if there is associated hypotension; short $t_{1/2}$ and twice-daily dosing
Dihydroindolone	Ziprasidone	Perhaps less weight gain than clozapine, parenteral form available	QT_c prolongation
Dihydrocarbostyril	Aripiprazole	Lower weight gain liability, long half-life, novel mechanism potential	Uncertain, novel toxicities possible

[1]Other aliphatic phenothiazines: promazine, triflupromazine.

[2]Other piperidine phenothiazines: piperacetazine, mesoridazine.

[3]Other piperazine phenothiazines: acetophenazine, perphenazine, carphenazine, prochlorperazine, trifluoperazine.

TABLE 29–4 Dose relationships of antipsychotics.

	Minimum Effective Therapeutic Dose (mg)	Usual Range of Daily Doses (mg)
Chlorpromazine	100	100–1000
Thioridazine	100	100–800
Trifluoperazine	5	5–60
Perphenazine	10	8–64
Fluphenazine	2	2–60
Thiothixene	2	2–120
Haloperidol	2	2–60
Loxapine	10	20–160
Molindone	10	20–200
Clozapine	50	300–600
Olanzapine	5	10–30
Quetiapine	150	150–800
Risperidone	4	4–16
Ziprasidone	40	80–160
Aripiprazole	10	10–30

◆ Drug Combination:

1.與 tricycline antidepressants

lithium

sedative drugs ——— 併用

Antipsychotic drug 會加強此三藥物之作用。

2.Antipsychotic drug 常引起 extrapyramidal toxicity，

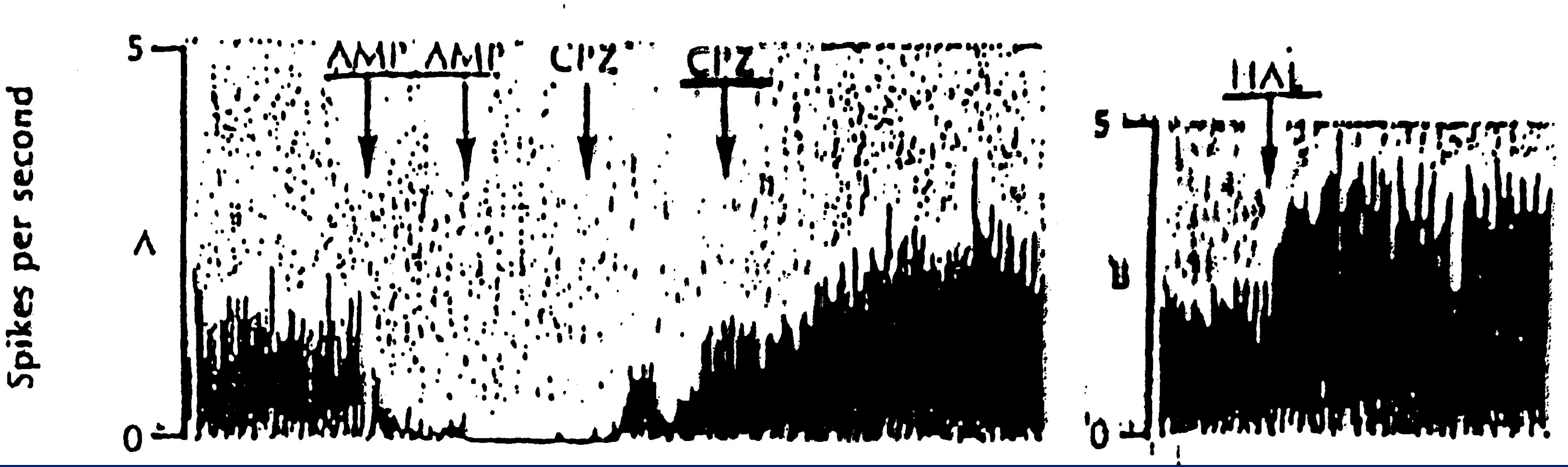
故與 antiparkinsonism drugs 併用。

3.由電生理的研究顯示

臨床上使用抗精神病藥之 potency與 DA neuron 之 firing rate↑有關。

(1) chlorpromazine可以對抗 amphetamine 所降低的firing rate.

(2) haloperidol 可增加 firing rate.


Spikes per second
5
A
0
AMP AMP CPZ CPZ
5
B
0
HAL

- **Drug Combination:**

4. 精神分裂病人，如配合使用tyrosine hydroxylase inhibitor

[Metyrosine(Demser)]

即可減少抗精神病藥物之dose。

5. Antipsychotic drugs與具下列作用之藥物併用，具加成作用。

sedative effects

alpha adrenoceptor-blockinng action

anticholinergic effects

thioridazine-quinidine-like action

•*ADVERSE EFFECTS*

Table 28-2.Adverse pharmacologic effects of antipsychotic drugs

Type	Manifestations	Mechanism
Autonomic nervous system	**Lose of accommodation(視力調節喪失), dry mouth, difficulty urinationg, constipation, mydriasis散瞳**	**Muscarinic cholinoceptor blockade.**
	Orthostatic hypostension, impotence, failure to ejaculate.	**Alpha adrenoceptor blockade.**

ADVERSE EFFECTS

Table 28-2. Adverse pharmacologic effects of antipsychotic drugs

Type	Manifestations	Mechanism
Central nervous system	**Parkinson's syndrome,** akathisia, dystonias.	**Dopamine receptor blockade.**
	Tardive dyskinesia (遲發性運動困難)	**Supersensitivity of dopanine receptors.**
	Toxic-confusional state.	Muscarinic blockade.
Endocrine system	Amenorrhea(月經閉止)-**galactorrhea (乳漏), infertility(不孕), impotence.**	Dopamine receptor blockade resulting in **hyperprolactinemia.**
Other	Weight gain	H_1 and 5-HT_2 blockade

遲發性異動症(Tardive dyskinesia)

一、臨床病徵及症狀:

1. 服用抗精神病劑6個月後出現，屬於抗神病劑的延遲性效應。

2. 症狀為頭部、四肢及驅幹呈現非自主性、不規則的舞蹈徐動狀的異常運動。

3. 典型表現有三群:

(1) 口頰舌症候群 (oral-buccal-lingual syndrome):口部周圍的異常運動，包括舌頭吐出及扭轉、厥唇、扮鬼臉。

(2) 遲發性肌張力異常 (tardive dystonia)、遲發性靜坐不能 (Tardive dyskinesia)。

(3) 遲發性抽動及顫抖(tardive tic and tremor)。

遲發性異動症 (Tardive dyskinesia)

二、流行病學

1. 接受過抗精神病劑治療超過一年以上的患者約有10-20%罹患TD。
2. 連續5年為20-26%。
3. 10年以上為49%。

三、病因學

1. D_2 receptor supersensitivity。
2. D_3 receptor 基因異常DRD3 (ser-gly)。
3. 在 subthalamic nucleus 的glutamic acid decarboxylase 活性降低。
4. 神經細胞毒作用:服用抗精神病劑可能產生自由基，進而 neurotoxicity。